SUPROFEN ESTERS AND AMIDES AS OPHTHALMIC ANTI-INFLAMMATORY AGENTS

This is a continuation of application Ser. No. 07/431,516 filed Nov. 3, 1989 now abandoned, which is a continuation of Ser. No. 07/241,759 filed Sept. 7, 1988, now abandoned, which is a continuation of Ser. No. 06/948,184, filed Dec. 31, 1986, now abandoned.

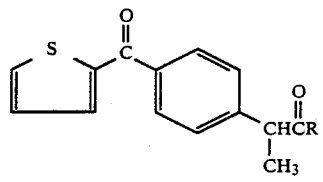
BACKGROUND OF THE INVENTION

This invention relates to certain esters and amides of suprofen having enhanced delivery characteristics on topical administration to the eye. This invention also relates to pharmaceutical compositions comprising such suprofen derivatives and to methods of using them when indicated to achieve an anti-inflammatory effect on topical delivery to the eye.

Suprofen, alpha-methyl-4-[2-thienylcarbonyl] benzeneacetic acid, is an inhibitor of prostaglandin biosynthesis with analgesic, antipurretic and anti-inflammatory properties. Suprofen was developed by Janssen Pharmaceutica; Beerse, Belgium, as disclosed in P. G. H. Van Daele, J. M. Boey, V. K. Sipido, M. F. L. De Bruyn, and P. A. J. Janssen; *Arzneim-Forsch, (Drug Res.),* 25 (10), 1495 (1975). This article is incorporated herein by reference to the extent that it teaches the preparation of suprofen and techniques of synthesis of certain esters and amides of suprofen which are described in that article, and which techniques, by analogy, provide an enabling disclosure on how to prepare the compounds of the present invention. The esters and amides of suprofen of the present invention are not disclosed by the incorporated by reference article and further the species disclosed in the prior art do not possess an attribute unique to the suprofen species of the present invention which property relates to their ability to be transported across the cornea and thus made available for the ophthalmic anti-inflammatory effect when administered to the eye. Beyond the disclosed original article relating to suprofen esters and amides, there appears to be no relevant prior art relating to suprofen derivatives and the ability of such suprofen species to be transported across the cornea for purposes of enhancing drug delivery. However, the use of suprofen per se and as complexed with certain xanthine derivatives for ophthalmic delivery for the purpose of achieving an anti-inflammatory effect is known. See for example, U.S. Pat. No. 4,559,343 which is directed to certain complexes of suprofen with xanthine derivatives for the indicated utility. This patent is incorporated herein by reference to the extent that its disclosure is relevant by analogy to an enabling disclosure of how to use suprofen, suprofen complexes, and suprofen derivatives and analogues in the treatment of ocular inflammation via topical delivery of pharmaceutical compositions comprising such suprofen entities.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of the invention may be described by the following formula:



(I)

wherein R is selected from the group consisting of alkoxyl and hydroxyalkoxyl of 3 to 8 carbon atoms and alkylamino of 3 to 8 carbon atoms. Especially preferred values for R include:

—OCH_2CH_2OH
—$OCH_2CH_2CH_2OH$
—$OCHCH_2CH_2CH_2CH_2OH$
—OCH_2CH_3
—$OCH_2CH_2CH_3$
—$OCH_2CH_2CH_2CH_2CH_2CH_3$
—$OCH(CH_2CH_3)_2$
—$NHCH_2CH_2CH_2CH_3$
—$OCH(CH_3)(CH_2CH_3)$

It has been found that when ocular inflammation is treated using the compounds and compositions of the present invention, that improved bioavailability is achieved as compared to suprofen.

The compounds of formula (I) are produced conventionally by reaction of suprofen and an excess of alcohol in an acid solution, preferably an HCl solution. The amides are formed by reaction of suprofen with the appropriate amine by known methods.

The following description is presented to illustrate the method of synthesis. The following procedure may be used to prepare all esters of suprofen (I):

A solution of 0.5 g suprofen, 0.5 mL of concentrated hydrochloric acid, and 10 mL of the appropriate alcohol are heated at 100° C. for 16 hours. The reaction mixture is allowed to cool to 22° C., and is then poured into a separatory funnel containing 20 mL of chloroform and 20 mL of 5% Na_2CO_3. The organic layer is separated and washed three times with 1N NaOH and three times with distilled water and then dried over magnesium sulfate. Evaporation of solvent gives the appropriate ester, which is purified by chromatography (30 g silica gel; 50% hexane, 50% ethyl acetate).

Suprofen 1-butyl amide may be prepared as follows:

To a solution of 0.50 g (0.00192 mole) suprofen, 0.28 g (0.00384 mole) n-butylamine, and 0.39 g (0.00384 mole) triethylamine in 100 mL methylene chloride is added 0.40 g (0.00192 mole) dicyclohexylcarboniimide. The reaction mixture is stirred at 22° C. for 48 hours, after which time the formed dicyclophexylurea is removed by filtration. The organic solution is washed three times with 0.1NaOH, and three times with distilled water, and dried over magnesium sulfate. The solvent is removed by evaporation, and the product which is obtained is isolated from ethyl acetate.

The preparation of other suprofen amides of structure I follows by analogy when an appropriate amount of the chosen amine is taken in substitution for the above illustrated 1-butyl amine.

Consistent with the teachings of the incorporated by reference U.S. Pat. No. 4,559,343, the ophthalmic anti-inflammatory derivatives of suprofen (I) can be used with the xanthine derivatives, and a representative formulation exemplifying the xanthine of choice, caffeine, which is given below. In the alternative, pharmaceuti-